REMARKS

Claims 1, 6 and 9-11 currently are pending in the application. Claim 2 has been canceled. Claim 1 has been amended. Support for the added language contained in claim 1 is found in canceled claim 2. No new matter has been added. In view of the foregoing amendments and following remarks, Applicants believe that all the rejections are in condition for withdrawal and that all pending claims 1, 6 and 9-11 are in condition for allowance.

35 U.S.C. § 112 Rejection

Claims 1 and 6 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserts, in pertinent part, that Applicants' specification only refers to one embodiment wherein the adjuvant is based on a mixture of cytokines and chemokines derived from supernatant collected from cultured human peripheral blood mononuclear cells (PBMCs) stimulated *in vitro* with antiCD3/CD28-coated beads. The Examiner therefore asserts that the embodiment is not commensurate with the entire scope of the claimed invention. The Examiner also asserts that the claimed method of enhancing an immune response to an antigen in a mammal comprising administering LCM as an adjuvant for the antigen does not correlate with the *in vitro* antigen stimulation of human PBMCs in the working example.

Claim 1 has been amended to recite the limitations contained in claim 2 (now canceled), namely, that the lymphocyte conditioned media are derived from naïve T cells cultured with antiCD3/CD28-coated beads. Applicants note that claim 2 is not part of this rejection. However, the Examiner's assertions would appear to include the limitations recited in claim 2 because claim 2 necessarily includes all of the limitations of its base claim. Thus, claim 2 implicitly recites an *in vivo* method of enhancing an immune response in a mammal. Therefore, if claim 1 as amended still is asserted to lack enablement with respect to an *in vivo* enhancement of an immune response in a mammal to an antigen and activated LCM, Applicants submit concurrently hereto supporting investigative data which provides evidence and corroboration that the invention is more than adequately enabled for the entire scope of the claimed invention, both *in vivo* and *in vitro*, and that one skilled in the art would be able to practice the claimed invention without undue experimentation.

Accompanying this Amendment is the signed Declaration of Dean L. Mann, M.D. Dr. Mann, a joint inventor of the present invention. A copy of Dr. Mann's curriculum vitae is attached hereto as Exhibit A.

Dr. Mann, as a specialist in the field of immunology and immunogenetics, attests, in Paragraph 3 of the Declaration, that it is his well-considered opinion that the invention is

more than adequately enabled for the entire scope of the claimed invention and that one skilled in the art would be able to practice the claimed invention in mammals *in vivo* as well as *in vitro* without undue experimentation.

To corroborate Dr. Mann's attestation, as described in Paragraph 4 of the Declaration, a scientific investigation was undertaken by the inventors of the instant application to determine whether the co-administration of vaccines with the activated lymphocyte conditioned media (LCM) of the present invention enhances T cell and antibody immune responses *in vivo* in non-human primates. A copy of a paper reporting this investigation is attached hereto as Exhibit B. The study utilized cryopreserved peripheral blood mononuclear cells (PBMCs) from immunized macaques.

As attested to in Paragraph 7 of the Declaration, comparison of responses in immune cells obtained at Day 35 in both the experimental group and the control group demonstrated residual T cell memory only in some of the animals in the experimental group which received vaccines combined with activated LCM. Additionally, antibody titers were greater at this time point and appeared to be sustained at higher levels in the monkeys receiving vaccine plus activated LCM. Indeed, Dr. Mann attests that one of the most convincing pieces of data that LCM acts to enhance immunity *in vivo* to a vaccine is the T cell responses observed to prostate specific antigen (PSA) in male monkeys. This is because PSA in non-human primates is closely related in its genetic sequence to the human counterpart that was used as an immunogen in this study.

Dr. Mann therefore concludes, at paragraph 8 of the Declaration, that the results from this investigation clearly show that the activated LCM of the present invention is more than adequately enabled for the entire scope of the claimed invention and that one skilled in the art would be able to practice the claimed invention in mammals *in vivo* as well as *in vitro* without undue experimentation.

Based on the foregoing evidence provided in the above-described expert's Declaration, Applicants submit that the claimed invention as claimed in claim 1 provides more than adequate enablement for one skilled in the art to practice the invention in patients *in vivo* without undue experimentation. Because claim 6 depends directly from claim 1, it too is adequately enabled. Applicants therefore request withdrawal of the rejection of claims 1 and 6.

35 U.S.C. § 112 Rejection

Claims 1 and 2 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner asserts that in claim 1, the term "lymphocyte-conditioned medium"

is indefinite because it is not clear what the active ingredient in the medium is that acts as an adjuvant and what the "condition" is for the process of making this medium. Additionally, the Examiner asserts that the term "antiCD3/CD28" is confusing because it can be interpreted as "CD3 and CD28" or as "CD3 or CD28."

Claim 1 has been amended to recite that the lymphocyte conditioned media are derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads. Additionally, Applicants submit that the nature of the lymphocyte-conditioned medium clearly is provided in the specification of the application as being an adjuvant derived from the supernatant material collected from *in vitro*-stimulated cultured human PBMCs (page 4, lines 16-18); and that the adjuvant is based on a mixture of cytokines and chemokines obtained from PBMCs stimulated with antiCD3/CD28-coated beads. Thus, the "condition" for the process of making this medium is the stimulation of PBMCs with antiCD3/CD28-coated beads, which leads to the release of cytokines and chemokines into the LCM, resulting in the LCM of the claimed invention. Applicants therefore respectfully request withdrawal of this rejection.

35 U.S.C. § 103 Rejection

Claims 1 and 9-11 stand rejected under 35 U.S.C. § 103(a) as being obvious over Baxevanis et al. in view of Setaluri et al. for the reasons previously made of record. Claim 1 has been amended to recite the limitations contained in claim 2 (now canceled), namely, that the lymphocyte conditioned media are derived from naïve T cells cultured with antiCD3- and CD28-coated beads.

The claimed invention is directed to a method of enhancing an immune response to an antigen in a mammal comprising administering to the mammal lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and CD28-coated beads in combination with a vaccine of the antigen.

In contrast, Baxevanis et al. disclose a method of adding supernatants collected from donor-derived PBMCs stimulated with anti-CD3 monoclonal antibody, but do not teach or suggest coating anti-CD3 onto beads. Setaluri et al. teach the dosage calculation and the administration of a tumor antigen hourly, daily, weekly, monthly or yearly by intramuscular or intravenous administration. Applicants submit that Baxevanis et al. do not teach or suggest a method of enhancing an immune response to an antigen in a mammal comprising administering lymphocyte conditioned media derived from naïve T cells cultured with antiCD3/CD28-coated beads in combination with a vaccine of said antigen to said mammal, and that Setaluri et al. do not cure this deficiency.

Applicants respectfully submit, therefore, that neither Baxevanis et al. nor Setaluri et al., either alone or in combination, teaches or suggests the claimed invention as claimed in claim 1. The features of dependent claims 9-11 are not asserted as independently establishing patentability apart from claim 1 from which they depend. Thus, claims 9-11 also are neither taught nor suggested by Baxevanis et al. and/or Setaluri et al. Applicants therefore respectfully request withdrawal of the rejection of claims 1 and 9-11.

35 U.S.C. § 103 Rejection

Claims 1, 2 and 9-11 stand rejected under 35 U.S.C. § 103(a) as being obvious over Baxevanis et al. in view of Setaluri et al. and Mengozzi et al. The Examiner asserts that, although Baxevanis et al. is silent as to the antigen to be administered with the activated PBMC supernatant, Setaluri et al. describe the dosage calculation and the time schedule and route of administration, and Mengozzi et al. disclose antiCD3/CD28-coated beads for *ex vivo* stimulation of T cells.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. *Id.*; *In re Fine,* 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious *unless the prior art suggests the desirability of the modification* (emphasis added). *In re Fritch*, 23 U.S.P.Q.2d at 1784; *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); *In re Gordon,* 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

As described above, the claimed invention is directed to a method of enhancing an immune response to an antigen in a mammal comprising administering to the mammal lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and CD28-coated beads in combination with a vaccine of the antigen.

In contrast, as described above, Baxevanis et al. disclose a method of adding supernatants collected from donor-derived PBMCs stimulated with anti-CD3 monoclonal antibody, but, as acknowledged by the Examiner, do not teach or suggest coating anti-CD3 onto beads.

Moreover, and more importantly, in contrast to the above-described claimed invention, Setalauri et al. is directed to the detection of microtubule associated protein-2

(MAP-2) as a marker to determine the metastatic potential of a tumor, including tumors derived from the neural crest such as melanomas, gliomas, Schwanomas, chromocytomas and small cell lung cancer. Additionally, Setalauri et al. disclose the use of MAP-2 to prevent tumor progression by increasing levels of MAP-2 protein in cells (column 2, paragraph 17). Thus, the disclosure of Setalauri et al. relates specifically to MAP-2 expression, and the finding that decreasing MAP-2 expression may prevent tumor progression in metastatic cancer cells. Furthermore, with respect to the assertion that Setalauri et al. disclose the administration of a tumor antigen, this is irrelevant to the claimed invention as claimed in claim 1, which is not directed to the administration of a cancer antigen, which is administered to increase levels of MAP-2 cells on a patient suffering from cancer, but rather to a method of enhancing an immune response in a mammal by administering an immunoenhancing lymphocyte conditioned media in combination with an antigen. Therefore, Applicants submit that the mere teaching by Setalauri et al. of a dosage calculation and the timing and route of administration of an antigen would not motivate one skilled in the art to combine this teaching, which specifically relates to determining metastatic potential of tumor cells by measuring MAP-2 expression in tumor cells, with the teaching of Baxevanis et al., which discloses a method of adding supernatants collected from donor-derived PBMCs stimulated with anti-CD3 monoclonal antibody.

Applicants therefore submit that if one skilled in the art were attempting to combine the teaching of Baxevanis et al. with the teaching of Setaluri et al. in the manner in which the Examiner has suggested, one could not do so without substantial destruction of the independent teachings of the references in a manner not suggested by the two references. Furthermore, even if one skilled in the art, with the improper use of hindsight, attempt to forcefit these fragmentary teachings into the combination suggested by the Examiner, one still would not have the teachings of Applicants' invention as currently claimed.

With respect to Mengozzi et al., this reference discloses coating beads with anti-CD3/CD28 for *ex vivo* stimulation of T cells. As such, therefore, Mengozzi et al. do not cure the deficiency described above, namely, the lack of a showing of an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead one skilled in the art to combine the relevant teachings of Baxevanis et al. with Setaluri et al. in the manner suggested by the Examiner.

Applicants respectfully submit, therefore, that Baxevanis et al., Setaluri et al. and/or Mengozzi et al. neither teaches nor suggests the claimed invention as claimed in claim 1. The features of dependent claims 9-11 are not asserted as independently establishing patentability

apart from claim 1 from which they depend. Thus, claims 9-11 also are neither taught nor suggested by Baxevanis et al. Setaluri et al. and/or Mengozzi et al. Applicants therefore respectfully request withdrawal of the rejection of claims 1 and 9-11. (Claim 2 has been canceled).

In view of the foregoing amendments and remarks, it is respectfully submitted that all pending claims 1, 6 and 9-11 in the present application comply with the requirements of Section 112 and are distinguishable from the cited prior art. Accordingly, reconsideration and withdrawal of the rejections and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

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